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Acute Skin and Pharynx Complications Following Adjuvant Hypofractionated Versus Conventional Radiotherapy in Patients with Breast Cancer

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ABSTRACT

Background: Hypofractionated radiotherapy (HF) method was introduced to overcome the quickly growing tumor cells as well as shortening whole treatment course in solid tumors such as breast cancers. Here, we compared the incidence of dermatitis and pharyngitis among patients undergoing HF versus conventional fractionationated (CF) radiation therapy following surgery for breast cancer.
Methods: During this prospective study, women who had undergone breast surgery since 2015-2017 were included in the initial sample population. 40 patients were included for analysis in each arm of CF and HF. Patients treated by CF received 50 Gy with 2.0 Gy per each fraction session and in group of HF; 42.4 Gy was delivered in 2.66 Gy per fraction sessions for 3 months. Severity of acute dermatitis and pharyngitis was recorded for all patients in both groups based on regular examinations during and after the radiation therapy.
Results: 18 out of 40 patients in the conventional group experienced dermatitis of which 11 and 3 were grade 2 and 3, respectively. In the HF group, 8 experienced only grade 1 acute dermatitis. Thus, acute radiation-induced dermatitis occurred more frequently (P=0.017) and more severely (P=0.002) in the conventional group within 3 months of follow-up. There was no statistically significant difference in incidence of pharyngitis between the two groups.
Conclusion: There was a statistically significant difference in occurrence of dermatitis between the two groups of conventional radiotherapy and those who received hypofractionated radiation. Incidence and severity of dermatitis was more common in those who received conventional radiotherapy in comparison to hypofractionated method.

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Introduction

Breast cancer (BCa) is the most common female non-cutaneous malignancy and is the first cause of cancer death in this gender.[1] Depression, anxiety and body image problems are some of the major psychological burdens of patients with BCa.[2-4] The psychological impact of a cancer in a mother most of all imposes stress on daughters and there is no relationship between the distress level and objective characters of the disease.[5,6] Depression and acute adverse effects can have a negative influence on patients' adherence to treatment.[7] These issues point out the importance of cosmetic outcomes of the treatments not only on the patient but also their family.

Radiotherapy following breast-conserving surgery has proven benefits in controlling the local disease recurrence and reducing the need for mastectomy.[8,9] The recommended dose for conventional radiation is a total dose of 50 Gy delivered in 25 fractions over 5 weeks. It is shown that administration of higher doses in fewer fractions [hypofractionated (HF)] has the same efficacy

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with less economic burden on health care system.[10] START-B trial investigated the efficacy of delivering an overall dose of 40 Gy over 15 sessions among women with early BCa. In contrast to the conventional radiation, this method resulted in less local recurrence and less adverse effects after 6-years of follow up.[11] Other studies have shown similar results with equal or superior efficacy of HF over conventional radiation for BCa with a clear margin and negative axillary lymph nodes (early-stage BCa).[12-15] HF radiation is associated with better patient adherence and compliance especially among the elderly, which significantly affects the recurrence rate.[16,17] Prolongation of the treatment period has a negative effect on the overall survival of early BCa patients.[18] Despite the benefits of HF methods, there are concerns about toxic effects of the higher doses of radiation per session in this method including, but not limited to, long term skin toxicity, cardiac effects in cases of left-sided BCa and lung fibrosis.[12,19,20] A 10-year follow-up of patients who underwent radiation in the START-B trial revealed that HF radiation causes significantly less skin changes.[11] However, there are some controversies on this issue.[12] We compared two common acute adverse effects of radiation therapy; dermatitis and pharyngitis between two radiation methods.

Materials and Methods

During this prospective study, patients who underwent adjuvant radiation therapy for BCa since March 2015-March 2017 were included. Inclusion criteria were female patients older than 18 years old with early invasive BCa with no distant metastasis who had already undergone surgery, either breast-conserving surgery or modified radical mastectomy. Subjects were examined on regular basis and were instructed to visit their physician if any complication was happened. The HF group was consisted of women with only early stage BCa who were defined as stage IA through IIB. Exclusion criteria consisted of male patients, locally advanced BCa, distant metastasis, patients referred for palliative radiation, existence of seroma or cellulitis following lymph node dissection and patients with any systemic disease that could slow tissue healing process (diabetes mellitus, severe anemia, collagen-vascular disease and severe dermatologic diseases with Koebner phenomenon). 80 patients of whom 40 had received conventional radiation (50 Gy in 25 fractions over 5 weeks) and 40 had received HF radiation (42.4 Gy in 16 fractions over 3.5 weeks) enrolled into the study. All patients were treated by 3D conformal method using 41-pairs multi-leaf collimator of ONCOR Siemens Linear Accelerators. For all patients, two physical wedges of 30-45 degrees were used for medial and lateral tangential fields. For supraclavicular fields two anterior-posterior beams were employed. As part of our hospital protocol for patients undergoing radiation, all patients were examined every week, 1 week after the last session, then every 3-4 weeks for 6 months to observe any possible adverse effect. Adverse effects were regarded as any complication observed during or within 3 months of completion of treatment. All patients were instructed to refer if any adverse effect was observed at the radiation site. Acute skin changes were examined by dermatology specialists in our department. The grade of skin toxicity and pharyngitis were reported using "Radiation Therapy Oncology Grading" criteria[21] (Table 1). Demographic data including age, past medical history, pathology of the tumor and lymph nodes, the method of the surgery, TNM staging of the tumor, the method of irradiation and whether there was a boost skin dose or not and documents of radiation-induced side effects (pharyngitis and dermatitis) were recorded in the relevant questionnaires.

All patients had signed written informed consent prior to inclusion into the study. The study was approved by ethics committee of Tabriz University of medical sciences. The study had no financial burden on the patients and all the examinations were performed as part of their routine care.

All the extracted data were analyzed using IBM SPSS Statistics, Version 22.0. Armonk, NY: IBM Corp. Chi-square test and Fisher's exact test were used to determine the relation between categorical variants. P-value of less than 0.05 was considered statistically significant.

The biologically effective dose (BED) for both regimens was calculated using the following equation:

$BED=E/\alpha=n.d(1+) - (T-T_k)$

Where E is the logarithm of total cell number, n is fraction number (16 for HF and 25 for conventional), d is radiation dose per fraction (2.66 for HF and 2 for conventional), T_p is the cell doubling time (2.5 days for skin and 3 days for tumor cells), T is the overall treatment time (22 days for HF and 43 days for conventional method) and T_k is the kick-off time (repopulation start time) (7 days for skin and 21 days for tumor).[22,23]

Results

Demographic data of our patients in both groups are presented in Table 2. There was a significant tendency to

Table 1: RTOG criteria for grading acute skin and pharyngeal radiation-induced toxicity[21]

Tissue	Grade 1	2	3	4
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Pharynx & esophagus	Mild dysphagia or odynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics / may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyper alimentation	Complete obstruction, ulceration, perforation, fistula

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Table 2: Demographic data in patients undergoing Hypofractionation *vs.* conventional radiation

	Conventional RT	Hypofractionated RT	P value
Sample size	n: 40	N: 40	
Age	49.86 ± 12.40 years (31-81)	44.46 ± 13.06 years (28-74)	0.208
Pathology			0.000
Invasive ductal carcinoma	36 (90%)	36 (90%)	
Invasive lobular carcinoma	4 (10%)	4 (10%)	
≥4 positive lymph nodes	24	0	0.001
(TNM) Tumor			0.602
1	14	12	
2	19	20	
3	5	8	
4	1	0	
(TNM) Lymph node			0.000
0	6	15	
1	8	25	
2	15	0	
3	9	0	
Surgery			
BCS	10	15	0.228
MRM	29	25	0.340
Boost dose	2	8	0.043

BCS: breast-conserving surgery, MRM: modified radical mastectomy

Table 3: The difference in acute radiation adverse effects between two groups

Adverse Effect	Conventional group frequency	HF group frequency	P value
Pharyngitis	6	4	0.499
Dermatitis	18	8	0.017
Dermatitis RTOG			0.002
I	5	8	
II	11	0	
III	3	0	
IV	0	0	

include patients with less number of involved lymph nodes in the HF radiation method rather than the conventional method. Although average age was not significantly different between the two groups, the HF group consisted of younger patients. This was a predicted finding following recommendations of previous trials that HF radiation is better to be used in younger patients with early stages of BCa.[12,18] The most common pathology was reported as invasive ductal carcinoma followed by invasive lobular carcinoma, which had an equal distribution among two groups and had no effect in radiation method selection. There was no significant difference in tumor size between two groups. Regarding the lymph nodes, there was a significant discrepancy with P<0.001 among two groups, which points to the importance of this criterion in the selection of the radiation method. The method of surgery was not significantly different between the two groups. Administration of boost doses was more common in HF radiation group (P=0.043). The acute adverse effects that were compared among two groups were radiation-induced pharyngitis and dermatitis (Table 3). Pharyngitis was more common in the conventional radiation group, but had no statistical significance. Dermatitis occurred more commonly and more severely in the conventional radiation group within 3 months of follow up and the results were statistically significant with P values of 0.017 and 0.002, respectively (Table 3).

Discussion

Our study showed that HF radiation causes fewer incidences of acute dermatitis. There was no evidence of superiority of the HF over the conventional method in terms of pharyngitis. Although the HF group received boost doses of radiation more frequently which could lead to dermatitis,[24] the fact is that the HF group experienced acute dermatitis less commonly with less severity. The reason for more frequent use of boost radiation in the HF group was the higher frequency of breast conserving surgery in this group in which, tumor bed boost radiation is recommended.[25,26] Lower adverse effect of HF method resulted in higher patient adherence and more patients completed their treatment course in the HF method. However, the data is not presented because some confounding factors are involved such as more advanced disease and weaker performance in the conventional group. If the HF method makes a positive effect on patient

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compliance, it can affect the local disease control.[16]

We investigated the concordance of physical concepts of hypofractionation with our clinical findings. BED represents the true biological radiation dose delivered to a tissue, which is manipulated by the combination of dose per fraction, total radiation dose and overall time of treatment and some tissue dependent factors such as kick-off time and tumor doubling time.

We investigated the effects of two radiation methods on the skin, using the formula for the BED of the skin. By accepting 10.6 and 11.2 Gy for α/β ratio to induce erythema and desquamation respectively,[27] BEDs of 30.92 and 41.6 Gy were calculated for conventional and HF radiation methods respectively. This conflicts the results from our and other studies. By using the above-mentioned equation in the calculation of tumor BED, the efficacy of the HF method (66.28 Gy) seems to be superior to that of the conventioanl method (57.29 Gy). This is in concordance with findings from large clinical trials with long-term follow up periods which have shown equal or superior efficacy for the HF method in local control of the disease in contrast to the conventional method.[8,12,17] It seems that BED equation may be only useful for prediction of long-term effects.

Factors implicated in poor cosmetic outcomes of HF radiation include administration of booster dose, associated diabetes mellitus, concurrent chemotherapy, regional lymph node irradiation, whole breast irradiation of more than 50.0 Gy and high body mass index.[7,24,28] In our study, the group received conventional radiation had significantly higher scores of lymph node involvement and had received more chemotherapy courses which could act as confounding factors and lead to bias in conclusion. One study has concluded that conventional fractionation carries a higher risk of moist desquamation of the skin in contrast to HF method.[28] Another study which followed the patients with breast cancer for 5 years concluded that HF radiation method with subsequent boost doses was as effective as conventional radiation in local control and survival while long-term cosmetic outcomes was not significantly different.[29] Another study comparing acute skin effects of patients with breast cancer concluded that at the third week of treatment, patients receiving HF radiation had more severe toxicity; whereas at the sixth week, the conventional radiation group experienced more severe skin toxicity. However, after 6 months, the outcome for both was similar.[30] Another survey showed that patients undergoing HF radiation had a better quality of life and experienced less fatigue and acute skin toxicity ithin 8 weeks after treatment.[31] Findings from another study are in favor of less acute dermatologic adverse effects in HF method.[32]

Other studies have evaluated the efficacy of HF method in other cancers. A retrospective study on patients with non-operable non-small cell lung carcinoma (NSCLC) showed lower incidence of grade ≥2 dermatitis following HF radiation (45 Gy at 3Gy per fraction).[33] A meta-analysis showed that HF radiation increases the 5-year survival by 30% in patients with NSCLC at the cost of increasing the risk acute esophageal toxicity.[34] A long-term follow-up of patients with non-operable early stage NSCLC undergoing HF radiation (48-60 Gy at 4 Gy per fraction) has also shown promising results.[35] In patients with rectal cancer, diabetes was a risk factor for more severe rectal bleeding following HF radiation.[36] Another study on these patients showed that neoadjuvant HF radiation was associated with slightly higher peri-operative complication rates.[37] Trials using the HF method (70 Gy at 2.5 Gy per fraction, 60Gy at 3Gy per fraction) for prostate cancer have demonstrated acceptable rectal and urinary toxicities after 2 and 5 years of follow-up.[38,39]

Conclusion

Our study showed a significant improvement in acute skin toxicity by HF radiation in contrast to conventional radiation method. There was no significant difference between the two methods regarding occurrence of pharyngitis. The important point is that all of the previous studies revealed superiority of HF radiation plus a tumor base boost dose in contrast to conventional radiation therapy in long-term follow-ups . Finally, it can be concluded that the HF method was shown to be tolerable in terms of acute skin acute complications and pharyngitis. For busy depatemtns, applying HF method provides a shorter treatment course (16 sessions instead of 25 sessions) and consequently more cost-effective treatments.

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Conflict of Interest: None declared.

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